wherein said vector contains more than copy of the nucleotide sequence encoding said epitope.--

REMARKS

Prior to entry of this amendment, claims 31-51 are pending in this Application. Upon entry of this amendment, claims 32-40, 42-46, and 48-54 would be pending. Applicants urge that the amendments to the claims introduce no new matter and do not raise new issues that would require an additional search or further consideration. There is adequate basis in the original claims as filed and throughout the specification to support these amendments. The entry of this amendment is therefor respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph – written description

Claims 33, 34, 43, 44, 49 and 50 are rejected under 35 U.S.C. § 112, first paragraph in view of the Office's determination that the specification fails to provide an adequate written description. Applicants respectfully traverse this rejection for the following reasons.

The Office relies upon *Regents of the Univ. Calif. v. Eli Lilly & Co.* (citation omitted), which held that claims drawn to human insulin cDNA supported by only a reference to the cDNA without disclosing the nucleic acid sequence or without disclosing further structure, function or formula failed to satisfy the written description requirement. In *Eli Lilly*, the patentee disclosed and claimed the sequence of rat insulin cDNA and the amino acid sequence encoded thereby but failed to disclose the cDNA nucleic acid sequence for human insulin. The *Eli Lilly* court held that the cDNA sequence encoding human insulin was not known at the time patentee filed its patent application. The written description requirement is designed to permit one of ordinary skill in the art to determine from the disclosure and claims as originally filed whether applicant was in possession of the claimed invention at the time of filing. The mere reference to human insulin cDNA, without "further structure, function or formula" failed to permit the skilled artisan to readily recognize that the inventor was in possession of the claimed human insulin cDNA at the time of filing the application.

The Office notes that DNA may not be defined merely by reciting its "principal biological property, i.e., tolerogenic epitopes of pollen, ragweed, dust mites, clotting factor VIII, acetylcholine receptors, collagen, myelin basic protein, thyroglobulin, and histocompatibility

antigen" (see: Official Action, at page 3, lines 3-6). However, the present disclosure does not seek to claim DNA by its "principal biological property" or by merely referring to other functional properties as was the case determined by the *Eli Lilly* court. The present disclosure provides an adequate written description of the claimed expression vector by teaching the various components of the vector from available sequences and components, where they may be found, how they may be assembled as well as a clear teaching as to their use in five working examples.

The specification further teaches, for example beginning at page 9, line 32 through to page 12, line 11, that a tolerogenic epitope of an antigen can be obtained and prepared by standard methods. The disclosure provides examples of antigen E of ragweed pollen, which was known in the art (Rafner *et al.* and Kuo *et al.*, each as cited at page 10, lines 12-15). Epitopes of antigen E have been identified (Olson *et al.* and Bond *et al.*, each as cited at page 10, lines 15-17). The disclosure further teaches that one of ordinary skill could identify DNA sequences encoding other antigens by searching databases, such as GenBank (see: page 10, lines 5-7). Also, the disclosure teaches that the amino acid of many of these antigens as well as epitopes of these antigens are known to those skilled in the art (see: page 10, lines 30-32). Further, the specification plainly states that the epitope and/or antigen can be a single epitope or it can be all or a portion of an antigen containing many epitopes, with an epitope interacting with T cells, or B cells or both (see: page 11, lines 1-10).

The selection of one or more epitopes is made based upon criteria disclosed in the specification, that includes, at least five factors. Epitopes are first selected for the ability to induce tolerance to the peptide or an antigen containing the epitope, preferably an antigen associated with an allergic response or autoimmune response. Secondly, if tolerance is desired to a large and complex antigen, more than one epitope can be selected to be combined into a fusion immunoglobulin. Preferably, the entire antigen may be included in the fusion immunoglobulin. Thirdly, epitopes may be selected if B and/or T cell tolerance is desired. Certain epitopes are known to those of skill in the art to be recognized by T cells and not B cells and vice versa. Fourthly, epitopes can be selected on the basis of reactivity with immune serum or lymphocytes from individuals having an allergic or autoimmune response to an antigen. For example, an epitope known to be immunodominant or to stimulate a strong autoantibody response can be selected so that the portion of the antigen included in the fusion immunoglobulin includes that

epitope. Fifthly, if there is little or no information known about epitopes on the antigen, it may be desirable to include the entire antigen in the fusion immunoglobulin (see: page 11, lines 11-33).

However, Applicants are not required to disclose what is already known in the art. Filed herewith are copies of publications which were available prior to Applicants' filing date. These publications are accession records to the GenBank and PubMed databases of the National Institutes of Health ("NIH"). These publications disclose a number of amino acid sequences and/or nucleic acid sequences encoding antigenic epitopes that would have been known and available to the skilled artisan at the time of invention. Specifically, these publications recite sequences for antigens or antigenic epitopes of: pollen, ragweed, dust mites, clotting factor VIII, acetylcholine receptors, collagen, myelin basic protein, thyroglobulin, and histocompatibility antigen.

In order to facilitate review by the Office, these nucleic acid sequences encoding epitopes that were available to the ordinary skilled artisan are provided in Table 1 of Exhibit A filed herewith, as an exemplary listing and not to be construed as exhaustive. Further, Applicants are not representing in Table 1 under "Published" that the date of publication is necessarily the earliest date the corresponding sequence was published. This date merely refers to a date of publication of at least one research journal article corresponding to the sequence identified below in the NIH accession record.

Therefore, Applicants have demonstrated that a number of antigenic epitopes were available in the art for use in the claimed expression vectors. This is clearly not the same fact pattern as the *Eli Lilly* court faced. The ordinary skilled artisan would have readily recognized from the specification that Applicants did provide an adequate written disclosure and that Applicants were in possession of the invention as presently claimed. Therefore, Applicants respectfully urge the Office to reconsider and now properly withdraw this ground of rejection.

Rejection under 35 U.S.C. § 112, first paragraph – enablement

Claims 33, 34, 43, 44, 49 and 50 are rejected under 35 U.S.C. § 112, first paragraph in view of the Office's determination that the claims are not supported by an enabling disclosure. Applicants respectfully traverse this rejection for the following reasons.

Applicants respectfully observe that the Office refers to the subject matter of the rejected claims as "tolerogenic antigens". However, the subject claims are drawn to expression vectors comprising tolerogenic epitopes obtained from antigens.

The present disclosure provides at least five working examples, in which vector constructs are prepared and employed resulting in immunological unresponsiveness in a mammalian host. Additional, the present disclosure enumerates a number of antigenic epitopes and their respective DNA encoding sequences that are useful candidates for construction of the presently claimed vectors and transformed hosts. Also, this disclosure makes clear that a number of genetic sequences useful in constructing the presently claimed vectors may be employed and as selected from multiple databases (see: the specification at page 9, line 32 to page 11, line 2). Further, the specification clearly teaches the skilled artisan how to select an amino acid sequence encoding an antigenic epitope (see: page 11, line 3 through page 12, line 11). Also, as discussed in regard to the grounds of traversing the previous rejection, the specification provides extensive guidance as to how to select and use desired epitope sequences, including in view of the number of antigenic epitopes that were available to the skilled artisan as provided in Table 1 of Exhibit A, filed herewith.

As the specification makes clear, a number of amino acid sequences encoding antigen epitopes may be used, therefore, it is not the epitope, but the construct, expression and presentation by the host cell that induces the immunological unresponsiveness and this, the specification clearly discloses and for which to the ordinary skilled artisan provides enabling guidance. Applicants therefore respectfully urge the Office to reconsider and properly withdraw this ground of rejection.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 31-51 are rejected under 35 U.S.C. § 112, second paragraph in view of the Office's determination that the claims are indefinite for failing to point out and distinctly claim the subject matter that Applicants regard as the invention.

The Office has determined that a number of terms render the claims indefinite. Applicants traverse this ground of rejection, however, in the interests of expediting the prosecution of this application, the claims have been amended to more clearly point out what Applicants regard as the invention. Applicants do not, by this amendment, surrender any subject matter, however. Applicants have not altered the scope of the subject matter as claimed, but more particularly point out what is claimed.

Further, Applicants respectfully urge the Office to reconsider its determination that the recitation of the term "autoantigen" renders the claims unclear or indefinite (see: Official Action,

page 6, last paragraph). While most mammalian subjects respond in varying degrees to different antigenic epitopes, autoantigen is, contrary to the Office's contention, an art recognized term and its use herein is consistent with such usage. For example, autoantigen is defined as: "[a] 'self' antigen; any tissue constituent that evokes an immune response to the host's tissues" (see: *Stedman's Medical Dictionary*, page 170, right column, fifth entry from bottom of page (26th Ed. Williams and Wilkins, Baltimore, MD)). Applicants respectfully urge that this rejection may now be properly withdrawn and entreat the Examiner to do so.

Rejection under 35 U.S.C. § 102(b)

Claims 31, 32, 37, 39 and 40 are rejected under 35 U.S.C. § 102(b) as being anticipated by Zambidis *et al.,* for the reasons of record as articulated in the previous Official Action. Applicants respectfully traverse this rejection for the following reasons.

The Office's primary premise for this rejection is to be found against the backdrop of the Office's broad interpretation of the claims. Under law, the Office is required to give the claims as broad an interpretation as is reasonable under the circumstances. However, the Office's overly generous interpretation of the claims is founded upon an alleged degree of indefiniteness which Applicants respectfully urge does not reside in the present claims. Therefore, it is no longer reasonable to consider that the cloned cI protein of bacteriophage lambda as taught by Zambidis *et al.* in any way anticipates the present claims, which are drawn to an expression vector comprising sequences, upon the expression of which in a host cell of a mammal induces immunological tolerance. The Office is, however, correct, in that the cI protein, as any protein, may result in an immunological response thereto by a host. However, Applicants urge that an immunological response is quite contrary to induction of immunological tolerance.

The Office further considers that the claimed expression vector is *inherently* anticipated by Zambidis *et al.* That is, the Office observes that the intended use of tolerance can be given little patentable weight in considering art rejections because use does not change the composition of the claims. While not embracing this broad view of the case law, Applicants respectfully point out that a claimed expression vector comprising elements, one of which provides that "wherein the expression of said vector in said haemopoietic or lymphoid cell of said fusion immunoglobulin induces immunological tolerance to said antigen epitope in said mammalian host" clearly distinguishes over the art. Such element is not merely intended use, but an inherent characteristic of the claimed composition. Zambidis merely notes that immuno tolerance studies

are underway. Applicants respectfully urge, therefore that the Office properly withdraw this rejection.

Rejection under 35 U.S.C. § 103(a)

Claims 31-33, 36, 37, 39-42, 45-48 and 51 are rejected under 35 U.S.C. § 103(a) as being rendered obvious and unpatentable over Zambidis *et al.* taken in view of Zanetti *et al.* and Chambers *et al.,* for the reasons of record as articulated in the previous Official Action. Applicants respectfully traverse this rejection for the following reasons.

The basis of this rejection again rests upon the determination, no longer existent (if in fact it ever really existed previously), that the claims due to indefiniteness permitted the combination of references as presented by the Office to support a finding of obviousness over Applicants' invention. The present claims, Applicants sincerely entreat, are clear and definite and do not support such a determination as posited by the Office that the construct of Zambidis *et al.* as discussed above, taken in view of the teaching of expression of proteins in T cells by Zanetti *et al.* combined with the expression of lymphokines in peripheral blood lymphocytes attributable to Chambers *et al.,* in any rational way even approximates the presently claimed invention.

Applicants have disclosed and herein claim an extremely novel and non-obvious method using the claimed vectors whereby such vectors comprising nucleic acid sequences, the expression thereof induces immunological unresponsiveness to antigen epitopes as encoded by the amino acid sequences on such vector in haemopoietic or lymphoid cells of a mammalian host. Applicants are puzzled (and awed) by the extraordinary leap of logic that the ordinary skilled artisan would be required to perform in going from the constructs of Zambidis *et al.* even taking, with charitable interpretation, the alleged teachings of expression of proteins in T cells by Zanetti *et al.* combined with the expression of lymphokines in peripheral blood lymphocytes attributable to Chambers *et al.* to arrive at the presently claimed vector and transformed host cells that induce immunological unresponsiveness.

The Office has failed to establish a prima facie rejection of the present claims by pointing to any reference that teaches or even suggests induction of immunological unresponsiveness. Certainly, the presently cited references are inadequate to sustain a proper prima facie rejection under the statute. Applicants respectfully request the Office to reconsider this ground of rejection and properly withdraw same and pass this application to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 308072000110. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: May 9, 2000

Respectfully submitted,

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EXHIBIT A

Table 1

PubMed Accession No.	Allergen	Source Organism	Nucleic Acid	GenBank Record No.	Published
Y12560	Pollen Bet v 4	*B.verrucosa*	mRNA	gi:2051992	1997
AR016640	Ragweed[1] Antigen E or Amb a I	Source of sequence unknown	DNA	gi:3972917	1998 (July 7)
U89793	Ragweed Amb a VI	*Ambrosia artemisiifolia*	mRNA	gi:1916291	1997
S03380	Dust Mite[2] Der p1	*Dermatophagoides pteronyssinus*	amino acid	gi:1078971	1989
D10499	Dust Mite Der f II	*Dermatophagoides farinae*	mRNA	gi:217307	1991
X15266	Acetylcholine Receptor (muscarinic acetylcholine receptor HM4)	*Homo sapiens*	DNA	gi: 32323	1987
CGHU3B	Collagen alpha 3 chain, type (IV) (Goodpasture antigen)	*Homo sapiens*	cDNA	gi:1360672	1994
S38729	p70 (Ku autoantigen)	*Homo sapiens*	mRNA	gi:250496	1992
NM_006501	myelin basic protein	*Homo sapiens*	mRNA	gi:5729930	1994
X05615	thyroglobulin	*Homo sapiens*	mRNA	gi: 37173	1987
Y07827	histocompatibility antigen (putative B7,3 molecule of CD80-CD60 protein family)	*Homo sapiens*	mRNA	gi:1770367	1997

[1] Sequence 79 from US Patent 5776761 (issued July 7, 1998)

[2] Also, see: Hoyne et al., *Immunology* 1993 Jan; 78(1):65-73; which teaches the immunological responsiveness of mice having differing major histocompatibility congenic strains to specified peptides representing the dust mite epitope of allergen Der p II